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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,767	07/03/2003	Fu-Sheng Wang	11333/20	4833

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,767	WANG ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8,10-14 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *8,12 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,10,11,13,14,23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 07/19/2010.Currently, claims 1, 3, 6, 8, 10-14, 20-25 are pending in the application.

Claims 1 and 23 have been amended. No claims have been newly canceled or newly added.

Claims 8, 12, 20-22 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected specie, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 05/18/2006.

Claims 1, 3, 6, 10, 11, 13, 14, 23-25 have been examined on their merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claim 1 is objected to because of the following informalities: It appears that the new limitation "though optics exclusively" is a typo and should be "**through** optics exclusively".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 10, 11, 13, 14, 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have entered the limitation "through optics exclusively" in claims 1 and 23. There is not sufficient support in the disclosure as originally filed for this limitation; thus it is being considered new matter. The disclosure as originally filed only supports the detection of megakaryocytes using those steps disclosed and does not provide an option wherein non-optical detection steps are excluded.

An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989).

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See,

e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir.1996).

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6, 10, 11, 13-14, 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (Sysmex Journal International 2000) in view of Houwen (US 5,830,701), Walters et al (Laboratory Hematology 2000), Ota et al (Haematologia 2000) and Sysmex Europe 2003 (Feb 2003).

Amended claim 1 is drawn to a method of detecting a megakaryocyte comprising: preparing an assay sample by combining a sample comprising a cell with a reagent comprising a polymethine dye, wherein the preparing does not involve an immunological method; detecting fluorescent light and scattered light emitted by the cell; generating a scattergram from the detected light, wherein the scattergram comprises a predetermined megakaryocyte region; and detecting the megakaryocyte through optics exclusively if a population exists in the predetermined megakaryocyte region of the scattergram generated from the detected fluorescent light and the detected scattered light, wherein the method executed by an automated hematology analyzer having the flow cytometer.

Claim 3 is drawn to wherein the detecting involves an automated hematology analyzer.

Claim 6 is drawn to wherein scattered light comprises side scattered light emitted by the cell.

Claim 10 is drawn to identifying the megakaryocyte region of the scattergram.

Amended claim 23 is drawn to a method of detecting a megakaryocyte comprising preparing an assay sample by combining a sample comprising a cell with a reagent comprising a polymethine dye and a hemolytic agent, wherein the preparing does not involve an immunological method; detecting scattered light and fluorescent light emitted by the cell; generating a scattergram from the detected light wherein the scattergram comprises a predetermined megakaryocyte region; and detecting the megakaryocyte through optics exclusively if a population exists in the predetermined megakaryocyte region of the scattergram generated from the detected fluorescent light and the detected scattered light, wherein the method executed by an automated hematology analyzer having the flow cytometer.

Claim 24 is drawn to wherein the scattered light comprises side scattered light.

Claim 25 is drawn to wherein the detecting involves an automated hematology analyzer.

Sakata teaches a method of detecting nucleated red blood cells (NRBC) with a reagent that comprises a fluorescent dye (polymethine) and a hemolytic agent and provides degree of cell staining information (p.41). Scattered light and fluorescent light are detected and a scattergram is generated (p.44). The detecting involves an automated hematology analyzer having a flow cytometer (XE-2100) (p.41). The preparing of the sample does not involve an immunological method. In addition, Sakata teaches that in the XE-2100, by developing and using optimum polymethine dyes not only for the NRBC channel, but also the 4 DIFF and RET channels, a wide variety of normal and abnormal cells can be classified and counted (p.42 column 2). Sakata also

teaches that the automated hematology counter will be able to count all types of cells-including, in the future, cells presently considered to be "impossible" to count (p.45).

Sakata does not teach the use of the method to detect megakaryocytes or to determine if a population exists in a megakaryocyte region of a scattergram.

Houwen teaches the use of the automated hematology analyzer, SE-9000 (column 7 line 51), for the detection of megakaryocytes (column 4 line 35) and for the determining of the region of the scattergram where the megakaryocyte population exists (column 7 lines 53-55). The use of a flow cytometer operating on an optical principle is taught as an alternative particle analyzer (column 7 line 17). Houwen also teaches that there is a great benefit to the medical field in monitoring of hematopoietic progenitor cells (which includes megakaryocytes) in peripheral blood stem cell transplantation (column 11 lines 1-4). Where the detecting comprises passing the assay through an electrically charged aperture and identifying a change in direct current (DC) resistance and radio frequency (RF) resistance is taught as well as cell size information based on a change in DC and cell interior information based on a change in RF (column 7 lines 2-23). Houwen teaches obtaining cell information about the treated blood sample using a particle analyzer and constructing a cell distribution profile (scattergram); delineating a portion of the profile as a zone in which at least one subclass of hematopoietic progenitor cells appear; wherein the profile zone is delineated through the use of a control sample comprising hematopoietic progenitor cells and counting the cells in the zone (column 11). Examples of the cell interior information include lateral (side) scattered light (column 7 lines 7-10).

Walters teaches that a comparison between hematology analyzers Sysmex XE-2100 and Sysmex SE-9000 showed excellent correlation for all parameters except number of basophils (p.89). Walters also teaches that the Sysmex XE-2100 has proven to be an accurate and precise high-speed analyzer and is suitable for both high volume laboratories and laboratories that test many abnormal samples (p.92).

Ota teaches that violet polymethine dye (VPM) is a megakaryocyte-specific stain that is clinically useful for estimating of megakaryocyte count, classification of megakaryocytes and identification of immature megakaryocytic cells (p.21).

Sysmex 2003 teaches the use of the Sysmex XE-2100 and the need for the recognition of platelets, giant platelets, megakaryocyte fragments and megakaryocyte nucleus (page 1).

One of ordinary skill in the art would have been motivated to use the optical method of Sakata for the detection of megakaryocytes because Sakata suggests that the method could be used for cell types other than NRBs (p.42 column 2 and p.45 column 1) and Houwen teaches that there is a great benefit to the medical field in monitoring of megakaryocytes (column 11 lines 1-4). The fact that Sysmex 2003 also teaches the need to observe and calculate megakaryocyte numbers along with the use of the XE-2100 would also motivate one of ordinary skill in the art to extend the use of this optical analyzer to include the monitoring of megakaryocytes as well.

One of ordinary skill in the art would have been motivated to identify a megakaryocytic region in the scattergram generated by the method of Sakata because regions for other cell types are also generated upon detection. One of ordinary skill in

the art would have been motivated to use side-scattered light when detecting megakaryocytes because Houwen teaches that this type of cell interior information is useful for detecting megakaryocytes. Using settings adjusted to display a megakaryocyte population would have been a matter of routine optimization since the artisan of ordinary skill would recognize that the results would depend upon optimal settings of the hematology analyzer and comparison with manual and flow cytometry results would have allowed reference controls to ensure accuracy. One of ordinary skill in the art would have had a reasonable expectation of success because Walters teaches that the Sysmex XE-2100 (used by Sakata) showed excellent correlation with the Sysmex SE-9000 (used by Houwen to detect megakaryocytes) and Ota teaches that a polymethine dye (also used by Sakata with the Sysmex XE-2100) is specific for megakaryocytes allowing detection of megakaryocytes as well.

Therefore, the combined teachings of Sakata, Houwen, Walters, Ota and Sysmex Europe 2003 render obvious Applicant's invention as claimed.

Claims 11, 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata (Sysmex Journal International 2000) in view of Houwen (US 5,830,701), Walters et al (Laboratory Hematology 2000), Ota et al (Haematologia 2000) and Sysmex Europe 2003 (Feb 2003) as applied to claims 1, 3, 6, 10, 23-25 above, and further in view of Tomer et al (Blood 1988).

Claim 11 is drawn to claim 10 wherein the identifying comprises 2 reference scattergrams, one with purified megakaryocytes and one substantially free of megakaryocytes and comparing them.

Claims 13 and 14 are drawn to claim 11 wherein the purified megakaryocyte comprises a cell induced from a CD34 positive hematopoietic cell by thrombopoietin.

Tomer teaches a method of detecting megakaryocytes that includes preparing an assay sample by combining bone marrow from normal human donors (p.1244 column 2) with fluorescent antibodies (dye) and a hemolytic agent (0.1% sodium citrate) (p.1245 column 1). Data collection of the fluorescence intensities and scattered light of each cell are carried out (p.1245 column). Scattergrams are generated by plotting scattered light and fluorescent light (p.1246 column 1). A megakaryocytic region is identified in the scattergrams by generating 2 reference scattergrams, one with purified megakaryocytes and the other without (p.1246 column 1). A population is determined to exist in a megakaryocytic region of the scattergram. The cell interior information is detected based on side-scattered light and the degree of cell staining information is detected based on fluorescent light emitted by the cell (p.1244 column 2). An automated hematology analyzer is also taught (p.1244 column 2).

Since Houwen teaches that the appearance zone of megakaryocytes is delineated based on the scattergram pattern for the appearance of megakaryocytes, one of ordinary skill in the art would have been motivated to include a reference scattergram without megakaryocytes as a negative control to improve the accuracy of the final result. One of ordinary skill in the art would have been motivated and had a

reasonable expectation of success because Tomer was using such a negative control to identify a megakaryocyte region on a scattergram as well.

The purified megakaryocytes are inherently induced from CD34 positive hematopoietic cells by thrombopoietin (TPO) and this induction occurs *in vivo*. Since the claim language does not require the induction to be *in vitro*, this meets the limitations of claims 13 and 14 as claimed.

Therefore, the combined teachings of Sakata, Houwen, Walters, Ota, Sysmex Europe 2003 and Tomer render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments filed 07/19/2010 have been fully considered but they are not persuasive.

Applicant argues that the Sakata reference in view of Houwen, Walters and Ota relate to nucleated red blood cell measurement and do not disclose Applicant's claimed invention.

This is not found persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The primary reference, Sakata, teaches the same method of detecting as Applicant and includes the use of the same apparatus (XE-2100) except for the type of cell to be detected. The secondary references, combined with the teaching of Sakata that the method could be applied to other cell types, provide motivation and reasonable expectation of success to apply the method of Sakata to the detecting of megakaryocytes as well. The method of Sakata uses the combination of fluorescent light and scattered light to detect nucleated red blood cells and suggests that this method be used to detect other cell types as well.

Applicant argues that the prior Office Action asserts the combination of a hypotonic solution with the method of Sakata while detecting cells through electrical resistance. Applicant asserts that the method of Sakata is not well suited for electrical resistance measurements and can cause cell damage and form changes.

This is not found persuasive as the obviousness rejection cited in the prior Office Action is not requiring that the method of detecting through electrical resistance be carried out with the apparatus of Sakata, but that the optical method of Sakata would be obvious to adapt for the optical detection of megakaryocytes based on the teachings in the prior art that suggest that it is desirable to detect megakaryocytes in a sample. Sakata teaches the required method steps for using the XE-2100 apparatus and also teach using a dye that is known in the art to be suitable for detecting megakaryocytes as well and suggest the detecting of other cell types in addition to red blood cells.

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the

claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The prior art has clearly suggested that methods of using cell detecting apparatuses can be modified to expand their abilities to detect different cell types.

The Supreme Court recently states in KSR v. Teleflex (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." See also M.P.E.P. §2141.

Clearly there was an identified need for the analysis of a megakaryocyte population in the art based on the art cited above and the knowledge available to carry out that analysis as well as the suggestion that the Sakata method could be modified to analyze other needed cell types as well.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg